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EXAMINER	
LAM, ANN Y	

ART UNIT	PAPER NUMBER
1641	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/627,447	HUANG, YADONG	
	Examiner	Art Unit	
	ANN Y. LAM	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 March 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 10-22* is/are pending in the application.

4a) Of the above claim(s) *15-18,21 and 22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8, 10-14, 19-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-8, 10-14, 19 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roses et al., 5,508,167, in view of Huang et al., "Apolipoprotein E fragments present in Alzheimer's disease brains induce neurofibrillary tangle-like intracellular inclusions in neurons", Proc. Natl. Acad. Sci. USA, 98:8838-8843, (2001).

As to claim 1, Roses et al. disclose a method for diagnosing Alzheimer's disease comprising detecting apoE4 in a biological sample (col. 2, lines 18-26; and col. 3, lines 55-58, and col. 4, line 35-45). Roses et al. teach that the presence of an apoe4 indicates that the subject is afflicted with Alzheimer's disease (col. 2, lines 23-25).

However, Roses et al. teach detecting apoE4 rather than carboxyl-terminal truncated apoE, as recited by Applicant. However, Huang et al. teach that carboxyl-terminal-truncated forms of apoE is found to be higher in patients with Alzheimer's disease than in normal patients (i.e., patients without Alzheimer's disease), (see abstract, and see page 8839, right column.) While Huang et al. do not specifically disclose that the presence of the carboxyl-terminal-truncated apoE can be used to

diagnose Alzheimer's disease, nevertheless, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the Roses et al. method to diagnose a patient to have Alzheimer's disease by detecting that carboxyl-terminal-truncated apoE level in the patient is higher than in a patient that does not have Alzheimer's disease because Huang et al. teach the correlation between the presence of a higher level of carboxyl-terminal-truncated apoE and the presence of Alzheimer's disease.). In other words, in view of the teachings of Roses et al. that the presence of an apoe4 indicates that the subject is afflicted with Alzheimer's disease (col. 2, lines 23-25), and that thus, a method for diagnosing Alzheimer's disease would comprise detecting apoE4 in a biological sample (col. 2, lines 18-26; and col. 3, lines 55-58), it would have been obvious to one of ordinary skill in the art to diagnose Alzheimer's disease by detecting carboxyl-terminal-truncated apoE because Huang et al. teach that the presence of carboxyl-terminal-truncated apoE level is found to be higher in patient's with Alzheimer's disease than in patients without the disease.

Moreover, as to claims 1-3, 19 and 20, while Huang et al. use carboxyl-terminated apoE obtained from cell cultures or brain tissues to show the correlation between carboxyl-terminated apoE and Alzheimer's disease, Huang et al. do not mention carboxyl-terminated apoE in other biological tissues or samples (specifically aqueous samples). However, it is noted that Huang et al. only utilizes samples from cell cultures and brain tissues but do not limit the discovered correlation to such samples. Huang et al. disclose that carboxyl-terminal-truncated fragments of apoE *are generated* inside cultured neurons and in Alzheimer's diseased brains, and Huang et al. utilizes

cultured cells and brain tissues from diseased individuals to perform the experiments. However there is no indication that the correlation discovered by Huang et al. are limited to carboxyl-terminal-truncated fragments of apoE in such samples. Furthermore, Roses et al. disclose that apoE are found also in blood, blood serum, blood plasma, cerebrospinal fluid, or other tissues (col. 9, line 66 – col. 10, line 2), and that apoE found in these samples can be used to as markers for the diagnosis of Alzheimer's disease (col. 3, lines 55-59.) Thus, Roses et al. suggest that regardless of where the apoE is synthesized, it can be used to diagnose Alzheimer's disease in the various biological fluids and tissues where it can be found. Because Roses et al. disclose that bodily fluids such as blood and cerebrospinal fluid as well as tissues contain apoE and can be used in diagnosing Alzheimer's disease, the skilled artisan would be suggested to detect in non-tissue samples also the carboxyl-terminated apoE as disclosed by Huang et al. as a marker for Alzheimer's disease. Moreover, it is understood in the art that such bodily samples can be obtained from living patients and are more readily obtainable than tissue samples or cell lysates, which provides a motivation for the skilled artisan to detect the carboxyl-terminated apoE in such fluid samples as a marker for Alzheimer's disease.

As to claim 4, the carboxyl-terminal truncated apoE has a molecular weight of about 14-20 kDa (page 8839, right column, second full paragraph).

As to claim 5, because it is not clear as to what fragment is being referred in claim 5 (see the 112, second paragraph rejection above), the carboxyl-terminal truncated apoE disclosed by Huang et al. (fragment with the molecular weight of about

14-20 kDa on page 8839, right column, second full paragraph) is deemed to be the carboxyl-terminal truncated apoE comprising amino acids 244-260 of apoE.

As to claim 6, apoE is apoE4 (see page 8840, right column; and page 8842, right column, first full paragraph; and page 8843, right column). (Huang et al. teach on page 8843, right column, that the study demonstrates that carboxyl-terminal truncated fragments of apoE induce NFT-like inclusions in neuronal cells and that both quantitative and qualitative differences in the abilities of apoE4 and apoE3 to induce these inclusions could contribute to the increased susceptibility of human apoE4 carriers to Alzheimer's disease. Huang et al. teach on page 8842, right column, first full paragraph, that carboxyl-terminal truncated forms of apoE3 and apoE4 induce NFT-like inclusions in neuronal cells. Thus Huang et al. make a correlation between carboxyl-terminal truncated apoE4 and Alzheimer's disease.)

As to claim 7, apoE is apoE3 (see page 8840, right column; and page 8842, first full paragraph; and page 8843, right column). (Huang et al. teach on page 8843, right column, that the study demonstrates that carboxyl-terminal truncated fragments of apoE induce NFT-like inclusions in neuronal cells and that both quantitative and qualitative differences in the abilities of apoE4 and apoE3 to induce these inclusions could contribute to the increased susceptibility of human apoE4 carriers to Alzheimer's disease. Huang et al. teach on page 8842, right column, first full paragraph, that carboxyl-terminal truncated forms of apoE3 and apoE4 induce NFT-like inclusions in neuronal cells. Thus Huang et al. make a correlation between carboxyl-terminal truncated apoE3 and Alzheimer's disease.)

As to claim 8, neither Roses et al. nor Huang et al. teach that the apoE is a mixture of apoE3 and apoE4. However Huang et al. teach on page 8843, right column, that the study demonstrates that carboxyl-terminal truncated fragments of apoE induce NFT-like inclusions in neuronal cells and that both quantitative and qualitative differences in the abilities of apoE4 and apoE3 to induce these inclusions could contribute to the increased susceptibility of human apoE4 carriers to Alzheimer's disease. Huang et al. teach on page 8842, right column, first full paragraph, that carboxyl-terminal truncated forms of apoE3 and apoE4 induce NFT-like inclusions in neuronal cells. Thus Huang et al. make a correlation between both carboxyl-terminal truncated apoE3 and apoE4 and Alzheimer's disease. It would have been obvious to one of ordinary skill in the art at the time the invention was made to assay for both, i.e., a mixture of, the carboxyl-terminal truncated apoE3 and carboxyl-terminal truncated apoE4 because Huang et al. make a correlation between Alzheimer's disease and the presence of both carboxyl-terminal truncated apoE3 and carboxyl-terminal truncated apoE4. The Office notes that Applicant's recitation of apoE encompasses carboxyl-terminal truncated apoE (and more specifically carboxyl-terminal truncated apoE3 and carboxyl-terminal truncated apoE4).

As to claim 9, the detecting step is detecting a level of carboxyl-terminal truncated apoE in the bodily fluid (see above regarding claim 2—blood or serum is bodily fluid).

As to claim 10, neither Roses et al. nor Huang et al. teach that the method further comprises detecting a level of full length apoE in the biological sample from the

individual; wherein a ratio of the level of carboxyl-terminal truncated apoE compared to the level of full length apoE in the biological sample that is greater than a ratio associated with a control biological sample from an individual not having Alzheimer's disease is indicative of a diagnosis of Alzheimer's disease. However, Huang et al. teach that full length apoE were found in normal subjects as well as Alzheimer's disease patients but that the carboxyl-terminal truncated forms of apoE fragments occurred to a greater extent in Alzheimer's disease patients (page 8839, right column). Thus, the data disclosed by Huang et al. show that the ratio of carboxyl-terminal truncated apoE fragments to full length apoE occur higher in Alzheimer's disease patients, because carboxyl-terminal truncated forms occur to a greater extent in Alzheimer's disease patients than in normal subjects while the full length apoE were found in both normal subjects as well as Alzheimer's disease patients. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made that the ratio of the level of carboxyl-terminal truncated apoE compared to the level of full length apoE in the biological sample that is greater than a ratio associated with a control biological sample from an individual not having Alzheimer's disease is indicative of a diagnosis of Alzheimer's disease because the data disclosed by Huang et al. disclose the correlation.

As to claim 11, the carboxyl-terminal truncated apoE has a molecular weight of about 14-20 kDa (page 8839, right column, second full paragraph).

As to claims 12, 13 and 14, neither Roses et al. nor Huang et al. teach that the ratio is greater than about 1.5 (as recited in claim 12), nor about 2 (as recited in claim

13), nor about 3 (as recite in claim 14). However, as discussed above regarding claim 10, it would have been obvious to one of ordinary skill in the art at the time the invention was made that the ratio of the level of carboxyl-terminal truncated apoE compared to the level of full length apoE in the biological sample that is greater than a ratio associated with a control biological sample from an individual not having Alzheimer's disease is indicative of a diagnosis of Alzheimer's disease because the data disclosed by Huang et al. disclose the correlation. While Huang et al. do not disclose the ratio being 1.5 or 2 or 3, however, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 105 USPQ 233. In this case, Roses et al. in view of Huang et al. disclose the general conditions of the claim (see above regarding claims 1 and 10), and thus discovering that the ratio of 1.5 or 2 being indicative of Alzheimer's disease requires only routine skill in the art under *In re Aller.*

Response to Arguments

Applicant's arguments filed March 17, 2008 have been fully considered. However, Applicant's arguments regarding the cited prior art are not persuasive.

Applicant points out that Huang et al. do not disclose or suggest that carboxyl-terminal truncated apoE would be present in a biological sample other than brain, and thus could be detected in a diagnostic test for AD. Rather Huang et al. teach that the

carboxyl-terminal truncated apoE is present in brains and lysates, of AD patients, and is present in intracellular inclusions. Applicant argues that thus the skilled artisan would not conclude that carboxyl-terminal truncated apoE would be present outside the brain, or in an aqueous biological sample.

Examiner notes that this issue is actually discussed in the grounds for rejection. Specifically, because Roses et al. disclose that bodily fluids such as blood and cerebrospinal fluid as well as tissues contain apoE and can be used in diagnosing Alzheimer's disease, the skilled artisan would be suggested to detect in non-tissue samples also the carboxyl-terminated apoE as disclosed by Huang et al. as a marker for Alzheimer's disease. Moreover, it is understood in the art that such bodily samples can be obtained from living patients and are more readily obtainable than tissue samples or cell lysates, which also provides a motivation for the skilled artisan to detect the carboxyl-terminated apoE in such fluid samples as a marker for Alzheimer's disease. There is no indication that the correlation discovered by Huang et al. is limited to carboxyl-terminal-truncated fragments of apoE in tissue samples or lysates. Rather the skilled artisan is suggested to detect for the carboxyl-terminal-truncated fragment in bodily fluids such as blood or cerebrospinal fluid since Roses et al. disclose that such bodily fluids contain the full length apoE, and the skilled artisan would have been motivated to detect the fragment in blood or cerebrospinal fluid as such fluid samples are well known in the art to be readily obtainable than tissue samples or lysates.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ann Y. Lam whose telephone number is 571-272-0822. The examiner can normally be reached on Mon.-Fri. 10-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ann Y. Lam/

Primary Examiner, Art Unit 1641